New and Notable

Tuning a Potassium Channel—The Caress of the Surroundings

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Rapid permeation of ions through membrane-spanning channels is only possible if the free-energy penalty for dehydration is effectively balanced by the free energy of binding within the channel. Channel selectivity arises if different ions have significantly different partitioning free energies. Potassium channels of muscle and nerve are exquisitely designed to select for potassium over sodium (1). This has traditionally been explained by noting that ligand coordination at the K⁺ binding sites mimics that in water and that channel binding sites form a rigid scaffold providing a "snug fit" for K⁺ but not the smaller Na⁺ (2,3).

Recent work has called these ideas into question. K⁺ has six waters in its canonical inner solvation shell, a structure markedly different from the eightfold carbonyl coordination of K-channels (4). Proteins are dynamic and their thermal fluctuations obscure size differences between K⁺ and Na⁺ (here coordination and selectivity are intimately dependent on electrostatic interactions among the binding sites' fluctuating carbonyl groups) (5), an idea with origins in Eisenman's explanation of the properties of glass electrodes (6). The same eightfold coordination environment that leads to high selectivity in nerve and muscle K-channels is essentially nondiscriminatory in NaK channels (7).

Submitted April 28, 2007, and accepted for publication May 15, 2007.

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Editor: Eduardo Perozo.

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In this issue, Varma and Rempe provide a novel explanation for these observations (8). Using quantum chemical methods, they analyze K⁺ and Na⁺ binding to clusters of water and of a few other ligands. Octa-coordinate channel binding sites are modeled as clusters of four glycine dipeptide moieties, thus mimicking the bidentate geometry that channel architecture imposes on neighboring intrastrand carbonyls while simultaneously allowing the interstrand carbonyl pairs to move freely. To discriminate between longerrange interactions contributing to bulk hydration (or channel solvation), they then embed these small clusters in different environments and carry out a series of gedanken experiments.

They find that preferred solvation structures, whether in water or in channel surroundings, are sensitive to their environment, providing new insight into factors controlling selectivity (5). In bulk water, with its high dielectric constant (ε), both K⁺ and Na⁺ prefer low coordination. However, if cationwater clusters could be embedded in low ε-surroundings, behavior would alter substantially, and higher coordination numbers would be favored. Since the surroundings can compete with the ion for ligation (by water in this case), provided they have hydrogen-bonding capacity, they can alter the structure of the solvent cage. Interestingly, the octacoordinate hydration cage does not match the channel's preferred ion ligation structure; to achieve selectivity K⁺ is overcoordinated.

Although the local ε in the vicinity of a channel binding site cannot be "tuned", the hydrogen bonding proclivity of its surroundings can be (and is, in physiologically relevant situations). In highly selective K-channels, there are no proximal H-bond donors to disrupt a binding site's solvation cage. In weakly selective K-channels, bioinformatic analysis shows that all have a common feature: H-bond donors near the selectivity filter (9). In fact, with sufficiently disruptive (high H-bonding

capacity) surroundings, like those found adjacent to all the octa-coordinating sites in the NaK channel (7), Varma and Rempe demonstrate that ion ligation at the channel binding site would change dramatically, accounting for hydration effects observed in the NaK system (10). The ion would bind five or six carbonyl oxygens in its inner solvation shell and K/Na selectivity would be lost.

What emerges is a hybrid between the "snug fit" and the "fluctuating structure" pictures. Ion binding sites in potassium channels are dynamic and thermal fluctuations do swamp ionic size differences; in octa-coordinate surroundings, electric field strength considerations from carbonyl ligands account for K/Na selectivity (5). However there must be sufficient structural rigidity to maintain the high (>6) carbonyl ligation environment. If this is lost, selectivity is lost as well. These ideas can be directly tested, and recent experimental data already lend support (11). They imply that K-channel selectivity behavior can be designed to order by site-directed mutations that introduce (or delete) H-bond donors near a K-channel selectivity filter.

This work was supported by a grant from the National Institutes of Health (GM-28643).

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